Defense Threat Reduction Agency

Basic Research Broad Agency Announcement

Webinar Briefing to Potential Applicants

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Research and Development Directorate
December 10, 2013

Purpose of Webinar

- Introduce/Reintroduce the Defense Threat Reduction Agency (DTRA)
- Introduce, discuss, and respond to questions on recently released amendment to Basic Research Broad Agency Announcement (BAA) and Service Call

Our goal is to inform prospective applicants about our BAA/Service Call and address their questions.

DTRA Mission

DTRA safeguards the United States and its Allies from Weapons of Mass Destruction (WMD) by providing capabilities to reduce, eliminate, and counter the threat and mitigate its effects.

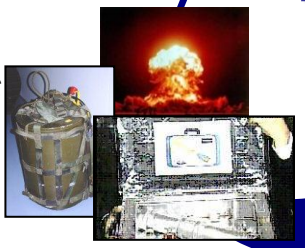
Chemical Weapons
... cheap and easy to make
... casualties not widespread

High-Yield Explosives
... easily available materials with many ways to deliver
… point targets

WMD THREATS

Biological Weapons
... use available technology
… attacks not quickly recognized, propagate with time

Nuclear Weapons
... difficult to acquire, devastating in use

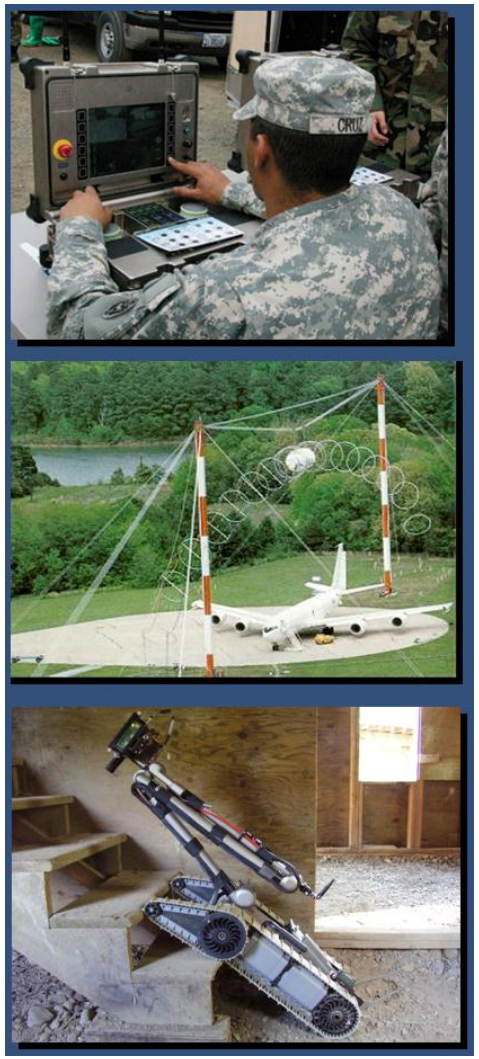


Radiological Devices
... dangerous to assemble with high contamination impact
… low lethality

Providing Solutions Across the Full Spectrum of Combating WMD

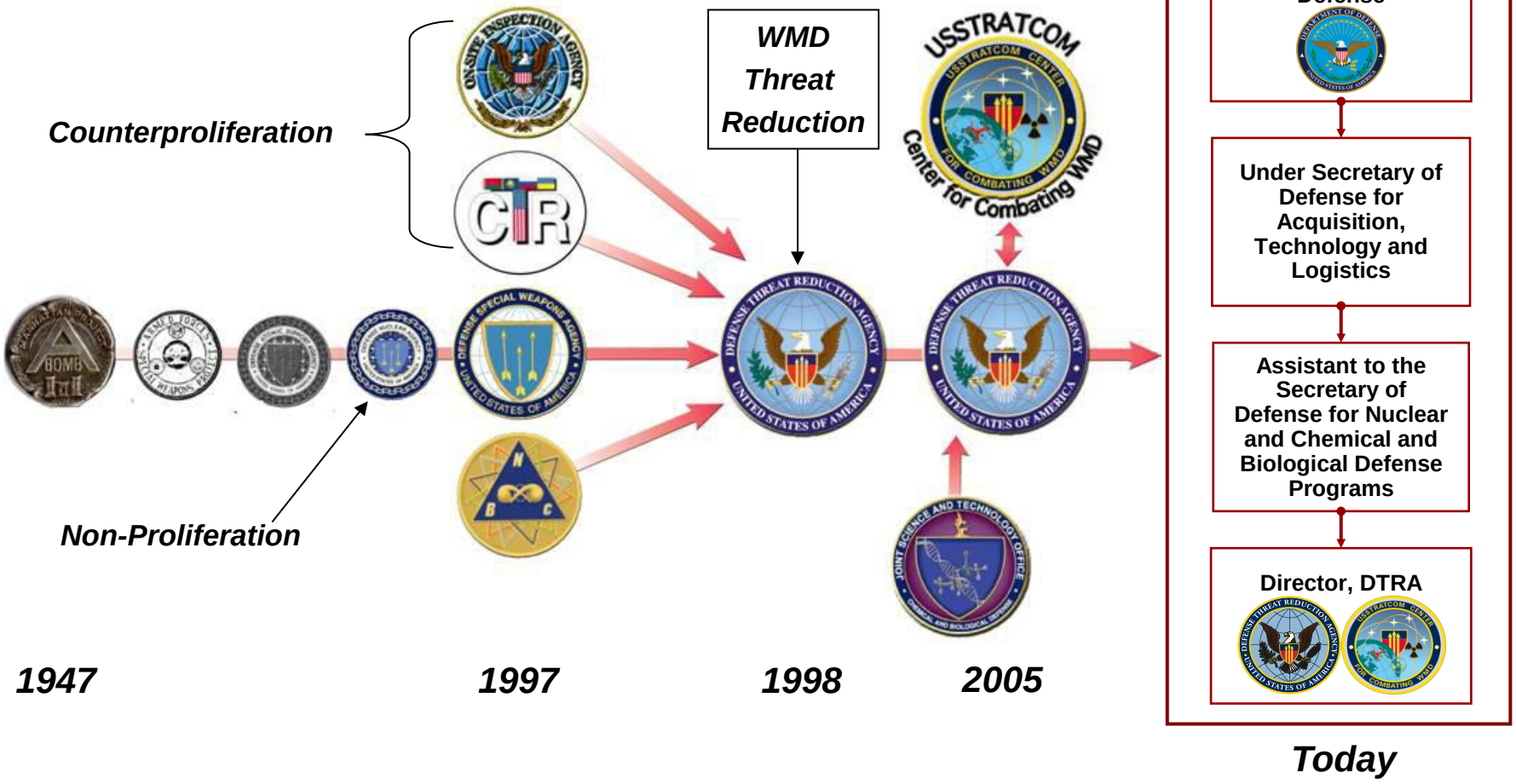
DTRA Attributes

- Combat Support Agency
  - Responsive to Joint Staff tasking
  - Military / Deployable Workforce
  - 24 / 7 Ops / Reach-back Center
  - Liaison Officers at all COCOMs
- Indigenous WMD field testing capability
- Limited laboratory infrastructure
  - Competitive = “Best of Breed”
- All appropriations under one roof
- Strong interagency ties – examples:
  - Department of Energy / National Nuclear Security Agency
  - Department of Health & Human Services (medical)
  - Department of Homeland Security (detection, borders)
  - Department of State (treaties, cooperative threat reduction)
  - Intelligence Community (collaboration)

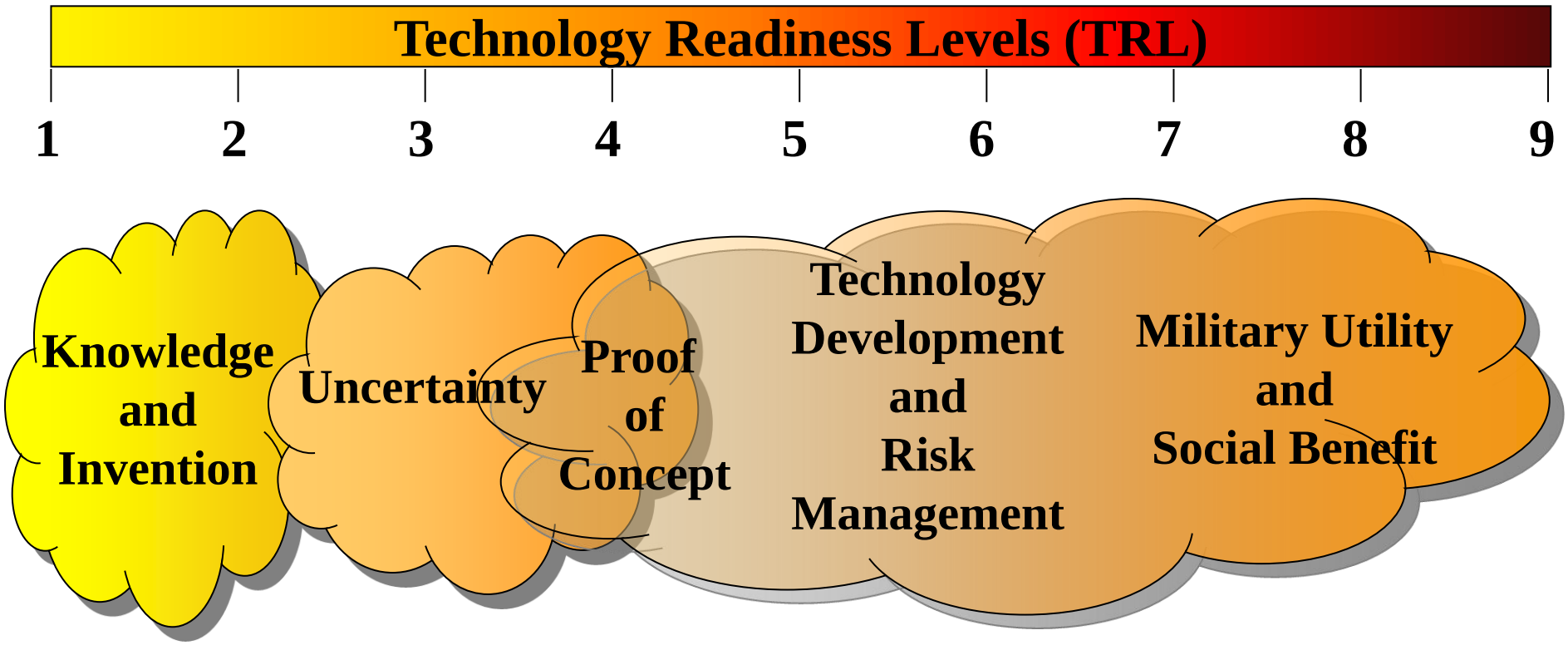


Aggressive Pursuit of Leading-Edge Capabilities

DTRA History

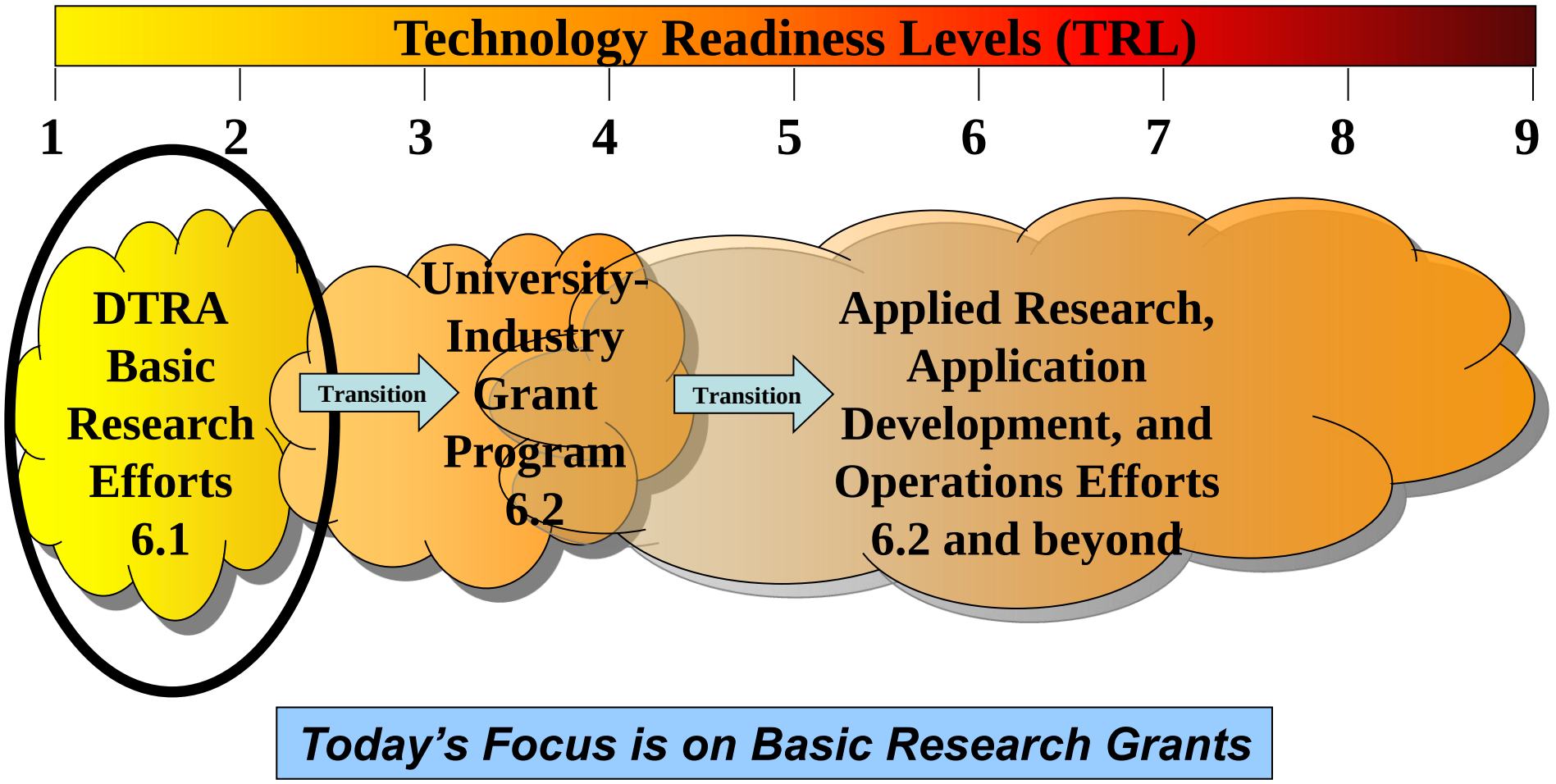


DTRA R&D Mission Space



DTRA Efforts Cover Entire Spectrum of Technology Readiness

Today's Focus is 6.1 Basic Research



Today's Focus is on Basic Research Grants

Expectations for Basic Research

- Publications and presentations
- Education of students, classes on C-WMD sciences
- Future assistance with peer-reviewing
- Timely, accurate invoicing and financial reporting
- Inventions and patent reporting using iEdison
- Annual progress reports and technical review participation
- Technology advancement to applied research when appropriate*
- Final Report

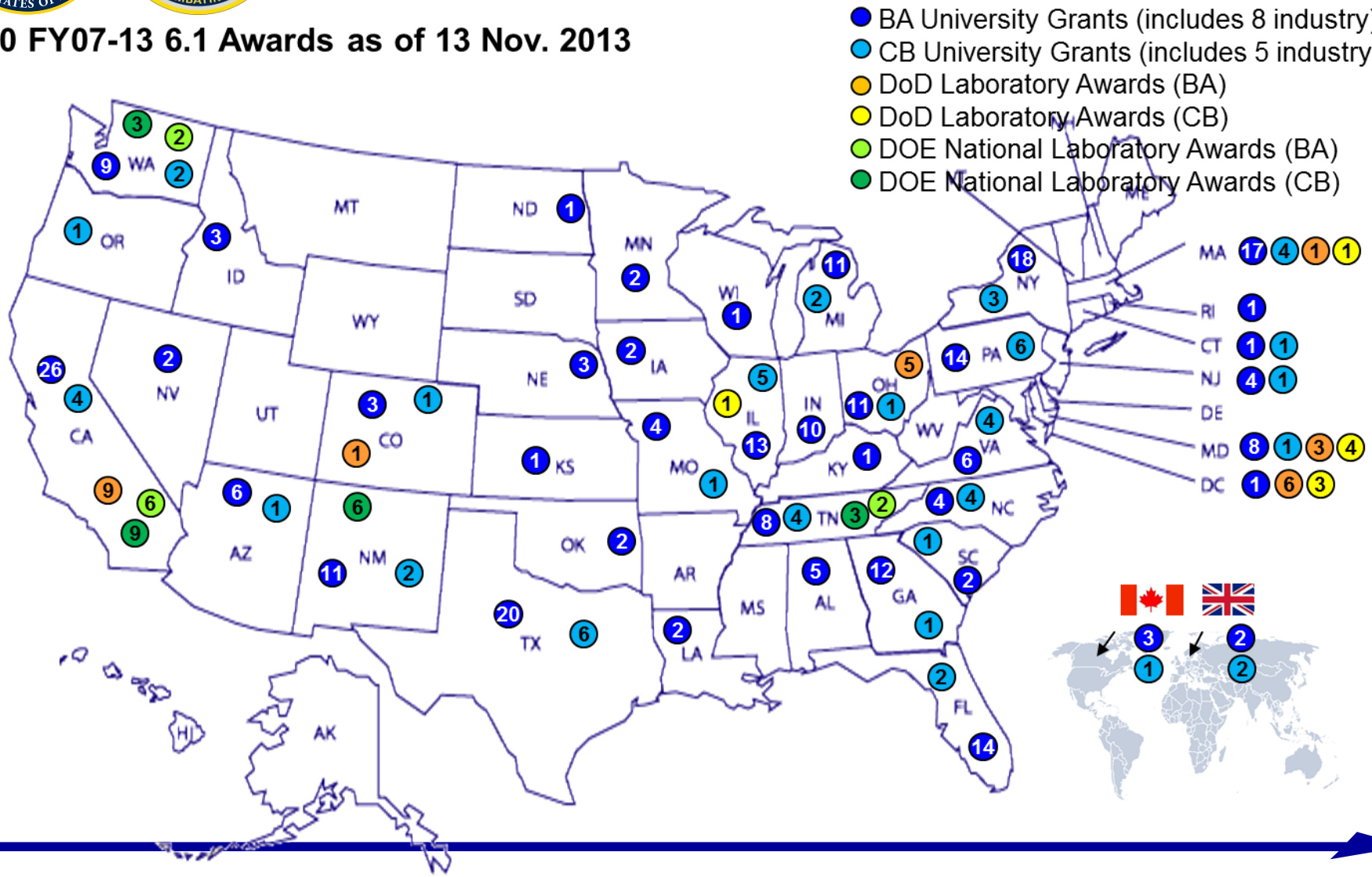
**The boundary between basic research and applied research occurs at the point when sufficient knowledge exists to support a hypothesis involving a specific application.*

Basic Research Thrust Areas

1. **Science of WMD Sensing and Recognition -** Generation of information that provides knowledge of the presence, identity, and/or quantity of material or energy in the environment that may be significant.
2. **Network Sciences -** Convergence of computer, information, mathematical, natural, and social science, including social networks and prediction of adversarial intent to employ WMD.
3. **Science for Protection -** Knowledge to protect life and life-sustaining resources including threat containment, decontamination, threat filtering, and shielding of systems.
4. **Science to Defeat WMD -** Phenomena that improves success of defeat actions (use of weapons) including explosives, accessing target WMDs such as bio agents and weapon modeling.
5. **Science to Secure WMD -** Environmentally responsible processes to secure, neutralize and control WMD and disrupt proliferation pathways.

Basic Research Awards 2007-2013

390 FY07-13 6.1 Awards as of 13 Nov. 2013



Current Basic Research Opportunity

Amendment 3 for Period D
of Basic Research Broad Agency Announcement
and Service Call
Released December 2nd

FY2011 – 2016 Basic Research for Combating Weapons of Mass Destruction (C-WMD) Broad Agency Announcement (BAA)
Amendment 3 (December 2013)
http://www.grants.gov
HDTRA1-11-16-BRCWMD-BAA

DoD Degree-Granting Academic Institutions
Amendment 3 (December 2013)
http://dtrasubmission.net
HDTRA1-11-16-BRCWMD-Service Call

White Papers Due January 13, 2014

Basic Research Broad Agency Announcement: Eligible Applicants

- **Pre-application white papers and proposals submitted will be considered from the following U.S. and foreign-based equivalents:**
  - Accredited degree-granting colleges and universities
  - Not-for-profit organizations/basic research centers*****
  - Industrial/commercial basic research centers, including small businesses with a portfolio predominantly in basic research*

  *****proposing a project with significant participation (minimum 30% of total effort value on the proposed project) by one or more accredited degree-granting colleges and universities; not eligible for the Young Investigator Program

- **The following entities may not participate as prime grantees for proposals, but may act as collaborators, including as Co-PIs, and/or subawardees:**
  - Federal laboratories, including DoD and Department of Energy (DOE) laboratories, Federal academic institutions, Federal agencies, and Federal organizations
  - DoD-and DOE sponsored Federally Funded Research and Development Centers (FFRDCs)
  - Foreign government-owned institutions
  - Industrial/commercial firms other than those described above

Basic Research Service Call: Eligible Applicants

- Pre-application white papers and proposals submitted will be considered only from the following:
  - DoD degree-granting academic institutions that are Federal government organizations, e.g. United States Military Academy at West Point, The Air Force Institute of Technology, etc.
- Subcontracting is permitted:
  - Sub-contracts may be used to carry out a portion of the research.
  - DTRA will review and consider the proposed sub-contracts for all applications on a case-by-case basis.

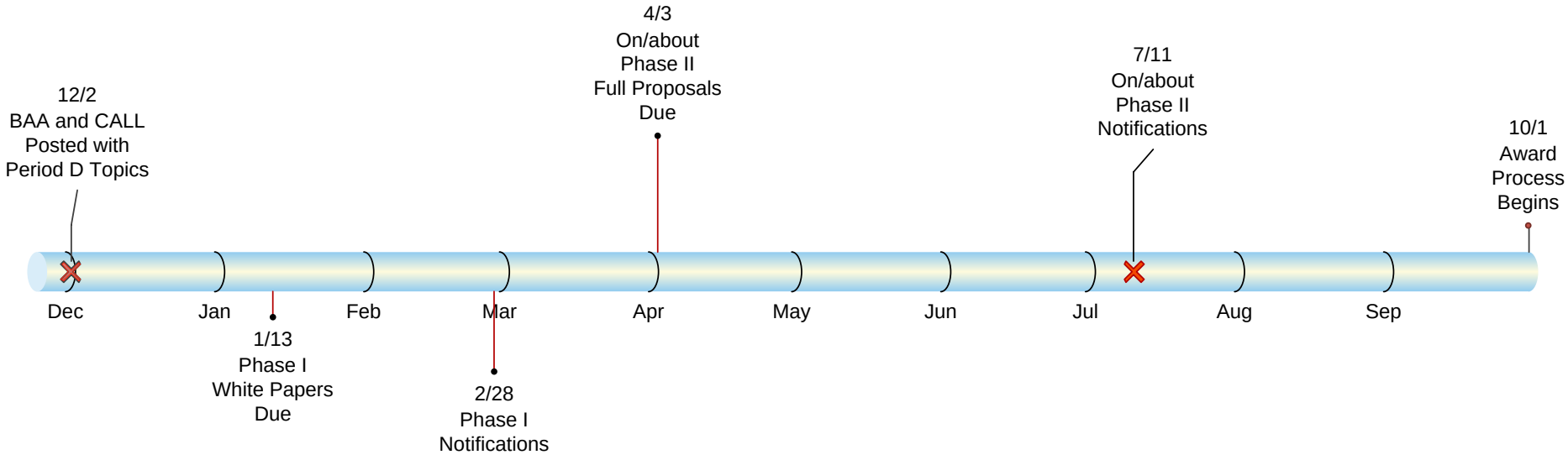
Award Value* and Structure

- BAA and Service Call Topics 1 – 11
  - Single Scope: Average $150K/year for 3 yrs + up to 2 option yrs
  - Multidisciplinary: Average $350K/year for 3 yrs + up to 2 option yrs
  - YIPs: Average $100K/year for 3 yrs + up to 2 option yrs

- BAA Topics 12 – 17
  - Single Scope: Up to $500K/year for 1 yr + up to 4 option yrs
  - Multidisciplinary: Up to $1M/year for 1 yr + up to 4 option yrs

All values are TOTAL (direct and indirect) grant values

Period D Time Line



Webinar Arrangements

- Next…Research Topic Presentations.
- After this presentation, questions will be addressed as time permits.
- This briefing and responses to questions submitted during this webinar session will be available through Grants.gov and dtrasubmission.net.
- Further questions can be directed to the points of contact indicated in the BAA and Service Call via e-mail.

BAA and Service Call Research Topics: DTRA Basic Research Needs

Topic 1: Refractory Debris Dissolution Techniques for Nuclear Forensic Field Procedures (Thrust Area 1)

Topic 2: Photodetectors and Solid-State Neutron Sensors for Radiation Detection (Thrust Area 1)

Topic 3: Sensing of Radiation Shielding Materials and Exploiting Interactions with Radiation from Radiological and Nuclear Sources (Thrust Area 1)

Topic 4: Development of Extremely Rapid Control Strategies for Mitigation of Cascading Failures on Multi-layer/Multi-dependent Dynamic Networks (Thrust Area 2)

Topic 5: Improved Semantic Analysis Theory to Identify WMD-Related Activities (Thrust Area 2)

Topic 6: Area of Responsibility Centric Cultural Modeling for WMD Threat Detection (Thrust Area 2)

Topic 7: Interrogation of Mechanisms for Cellular Resistance to Radiation Damage using Melanized Fungi as Model Systems (Thrust Area 3)

Topic 8: Basic Science of Radiation Effects in Micro/Nanoelectromechanical Systems MEMS/NEMS (Thrust Area 3)

Topic 9: Crustal-Earth Materials and Manufactured Materials under Dynamic Extremes (Thrust Area 4)

Topic 10: Energetic Materials for CWMD (Thrust Area 4)

Topic 11: Smart Materials with Unconventional Indicators for Facility Access Denial and Security of WMD Materials (Thrust Area 5)

Topics 1-11 are also solicited as Young Investigator Program (YIP) Topics

BAA and Service Call Research Topics: JSTO-CBD Basic Research Needs

Topic 12: Fundamental Understanding of in vitro Glycosylation: Methods, Stability, Immunogenicity, and Efficacy of Therapeutic Glycoproteins (Thrust Area 3)

Topic 13: Predictive Understanding of the Blood-Brain Barrier in Threat Environments (Thrust Area 3)

Topic 14: Bio-inspired Catalytic and Binding/Reporting Systems for Chemical/Biological Defense (CBD) (Thrust Area 3)

Topic 15: Ambient Surface Chemistry of Chemical Warfare Agent (CWAs) Air Purification Filtration Materials (Thrust Area 3)

Topic 16: Gene Amplification and Overexpression: Novel Mechanisms of Multidrug Resistance (MDR) Phenotypes (Thrust Area 3)

Topic 17: WMD Signal Transducer Toolkit for Synthetic Biology Applications (Thrust Area 3)

Topics 12-17 are <u>not</u> available as Young Investigator Program (YIP) Topics

Topic 1: Refractory Debris Dissolution Techniques for Nuclear Forensic Field Procedures

Objective: Explore ways to dissolve post-detonation debris from a nuclear event using environmentally friendly, potentially field deployable, techniques on a reasonable time scale (<15 hour total dissolution time for a 5-10g sample), and/or a qualitative understanding of the impacts of various dissolution approaches on the fidelity of analysis. Interests include investigation of non-hazardous chemical dissolution, techniques mating fieldable instrumental dissolution assistance with chemical techniques, and an understanding of the fundamental phenomenology of such dissolution methodologies on the quality of measurements.

Research areas could include:

- Organic or inorganic methods to completely dissolve high-pressure, high-temperature, refractory debris with environmentally friendly chemicals
- Physically assisted methodologies for dissolving refractory debris such as microwave, sonic, or photon techniques

Picture courtesy of chemicallabels.com

Topic 2: Photodetectors and Solid-State Neutron Sensors for Radiation Detection

Objectives:

- Explore novel methodologies and phenomenologies which will improve how neutrons or gamma rays are sensed and recognized from radiological and nuclear materials of interest.
- Neutron-sensing materials must aspire to include the following characteristics: fast response times, excellent neutron-gamma discrimination, non-toxicity, low noise, and an ability to perform neutron spectroscopy.
- Photodetectors should have high quantum efficiencies in the wavelength region that is typical of current scintillators (near blue to deep ultraviolet).

Research areas:

- New ecomimetic materials for photodetection
- Solid-state, direct conversion neutron sensors
- Organic or polymer-based materials for photodetection
- Methodologies being investigated for solar cells, such as plasmonic nanostructures or Mott insulators

Not interested in:

- Advancing existing detectors
- Geometrically scaling down current detection systems or methodologies
- Solid-state indirect conversion heterostructures for neutron sensing

Helium-3 neutron detectors

Scintillators with Photo-multiplier tubes

Pictures courtesy of Saint-Gobain

Topic 3: Sensing of Radiation Shielding Materials and Exploiting Interactions with Radiation from Radiological and Nuclear Sources

Objective: We seek basic research that will significantly improve our understanding of directly identifying shielding materials. Novel ideas that enable identification of unique signatures which exploit radiation interactions (from RN materials) with shielding materials are also desired.

Research areas could include:

- Investigate accumulation of interfacial defects at high-Z and low-Z material boundaries
- Approaches for characterization of atoms or molecules to assist in remote sensing of shielding materials
- Novel characterization of unique signatures of shielding materials
- Novel sensing based on quantum properties or atomic interference to detect particles, electro-magnetic radiation, gravity, or motion
- Interactions & properties of quasiparticles and quantum condensates leading to sensing mechanisms
- Identification of novel signatures via high precision metrological techniques in microwave to UV frequencies

Lead is a commonly used material for shielding of gamma rays and x-rays.

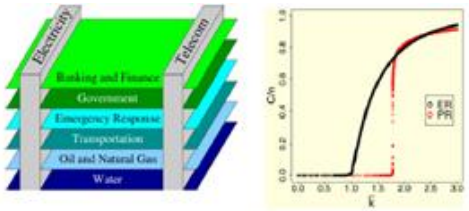
Source: *http://en.wikipedia.org/wiki/Lead_shielding*

Topic 4: Development of Extremely Rapid Control Strategies for Mitigation of Cascading Failures on Multilayer/Multi-dependent Dynamic Networks

Objective: Extend prior network theory research to develop strategies that rapidly control the onset of pre-cascade behavior before the networks decay into full blown cascading failure. The emphasis is on sub-second response, coupled pre-planning and active rapid control strategies, and large realistic synthetic environments for prediction and control of the cascading failures that result from WMD attacks.

Research areas could include:

- Exploitation of currently available sensor information to observe network states under WMD attack
- Sub-second network computations to enable decisions concerning real-time minimization of network instability
- Novel advancements in adaptive/computer relaying and other wide area measurement methods to rapidly reconfigure loads
- Novel graph theoretical methods to incorporate distributed real time assessment of the network to be controlled
- Theoretical understanding of novel point protection or other stabilization devices on overall network resilience/ robustness
- Optimal rapid and/or intelligent islanding/load shedding to limit a cascade affected area.



Layers of interdependent infrastructure networks. Each network on its own may exhibit complex phase transitions in behavior, yet the coupling between them is largely unexplored.

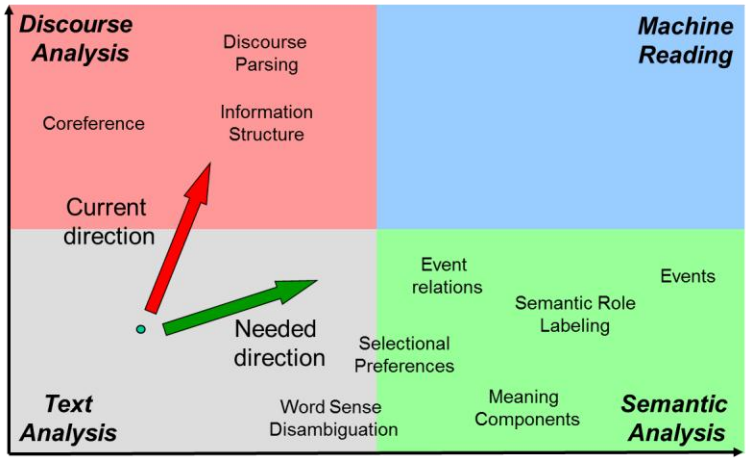
Example of a power grid cascade –
5 rounds initiated by a 50km radius attack in the LA area

Topic 5: Improved Semantic Analysis Theory to Identify WMD-Related Activities

Objective: Advance the fundamental understanding and discover improved methods to accurately analyze WMD events. Proposed research may extend existing approaches, but preference will be given to developing innovative methods that mirror linguistic structures and lexicographic resources in new ways. Main thrust of this topic is to discover innovative and novel new automatic lexical acquisition approaches to improve semantic analysis on both lexical and predicate-argument structure levels. Areas of interest (not independent but built upon each other) are representation, identification and interpretation.

Research areas could include:

- Develop novel lexicographic resources to include both semantic and quantitative information
- Contextual & distributional analysis to automatically extract semantic representation from corpora
- Novel development of representational learning (e.g. deep learning) to represent semantic features such as meaning components & selectional preferences
- New methods to rapidly and accurately relate semantic findings to language processing; this area should build on the foundation of the other three areas, and only enter in during later years

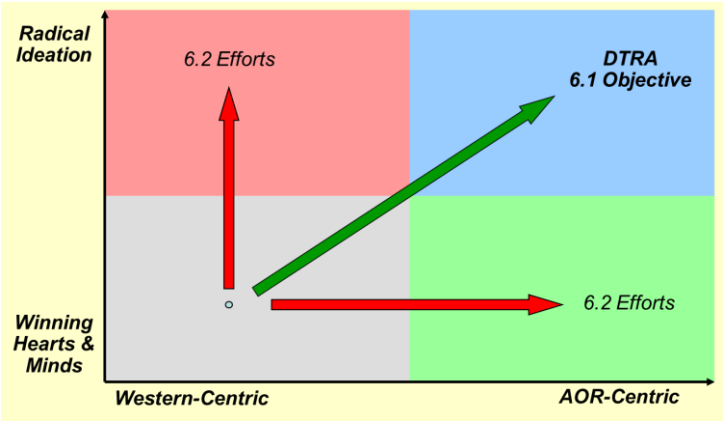


Topic 6: Area of Responsibility-Centric Cultural Modeling for WMD Threat Detection

Objective: There are two main objectives of this research program: 1) validate (or invalidate) current generic models for social networks or social influence with data derived from populations across the varied AOR of the Combatant Commanders, and 2) where these models are explicitly shown to be invalid, expand mathematical, statistical, and analytical techniques to understand and represent the specific cultural factors and behaviors of those populations.

Research areas could include:

- Culturally & Regionally Dependent Social Network topography and evolution whether of the network or of information and influence using network as a medium
- Culturally & Regionally Specific Socio-cognitive models of radicalism or other extremist behavior that relate to the use or pursuit of WMD
- Culturally & Regionally Specific Integration of operational and technical capacity with knowledge of motivation and intent without losing meaning
- Culturally & Regionally Aware Computational algorithms and methods that allow for culturally dependent variable incorporation and validation

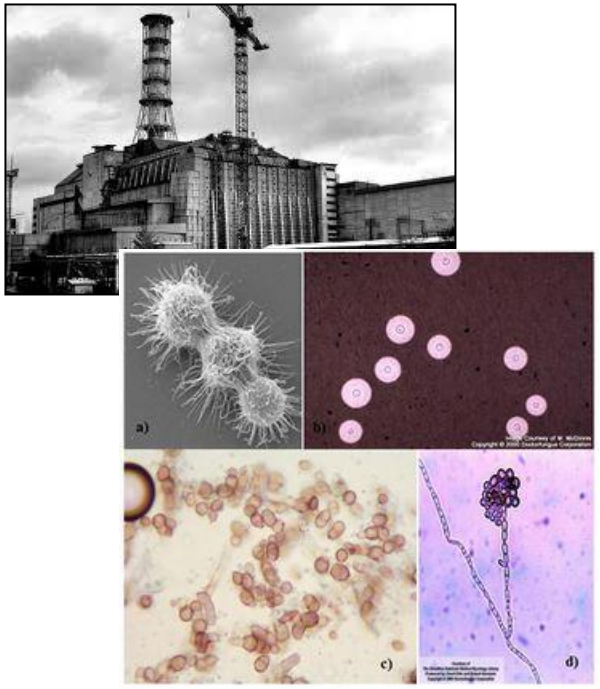


Topic 7: Interrogation of Mechanisms for Cellular Resistance to Radiation Damage using Melanized Fungi as Model Systems

Objectives: Identify and characterize mechanisms of resistance to ionizing radiation in melanized fungi. Competitive responses will interrogate multiple mechanisms in order to develop holistic knowledge of cellular response to ionizing radiation. Whole genome sequencing of melanized fungi is not of specific interest.

Research areas could include:

- Identify means by which cells sense radiation and transform signals into recognizable inputs
- Investigate identity and nature of intracellular radioprotective chemical species
  - Elucidate mechanisms of protection
  - Identify necessary location of action
- Characterize mechanisms and pathways activated following radiation exposure
- Determine whether mechanisms extrapolate to other cell lines & whole animal systems



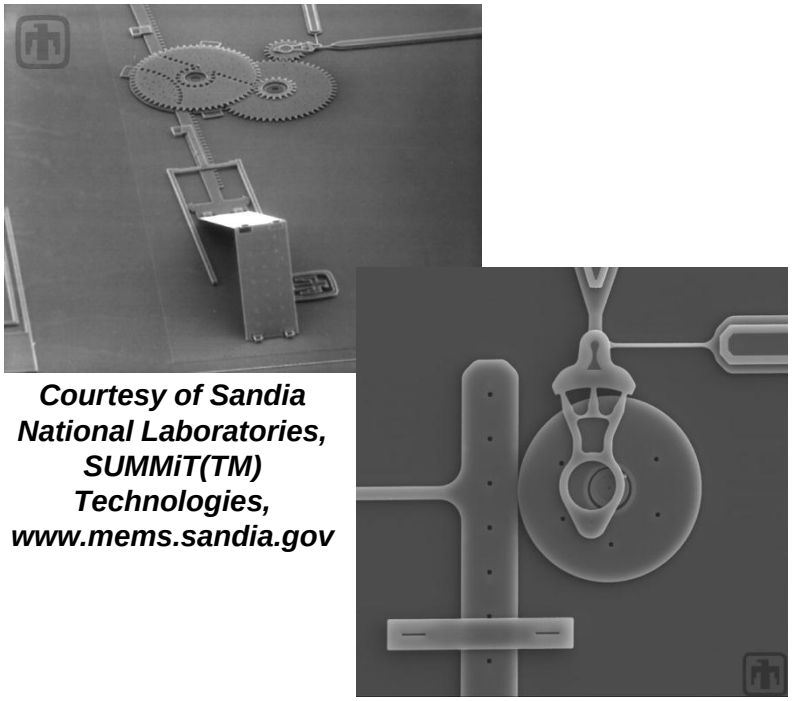
Topic 8: Radiation Effects in MEMS/NEMS

Objectives:

- Investigate the effects of radiation (gamma, x-ray, ion, neutron, and high energy electron) on micro/nanoelectromechanical systems (MEMS/NEMS) and mechanical logic devices. Of particular interest are advanced devices employing **thin films, small feature sizes, novel designs, or other advanced technologies**.
- Apply knowledge base of radiation effects in silicon microelectronics to state of the art MEMS/NEMS and mechanical logic devices.

Research areas:

- Radiation effects in:
  - Thin film MEMS
  - NEMS
  - Mechanical Logic Device (micro/nano scale)
  - Piezoelectronic transisters
- Not interested in:
  - Support electronics
  - Device development
  - Microfluidic devices



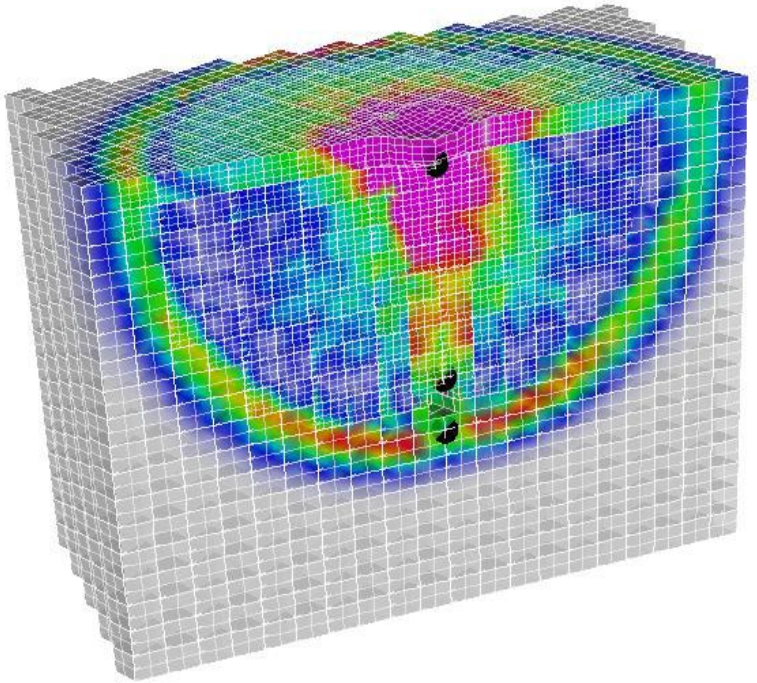
Courtesy of Sandia National Laboratories, SUMMiT(TM) Technologies, www.mems.sandia.gov

Topic 9: Crustal-Earth Materials and Manufactured Materials under Dynamic Stress

Objective: Experimental and computational basic research to significantly improve our understanding of the effects of high-dynamic compression and tension on highly-heterogeneous crustal-earth and manufactured materials.

Research areas could include:

- Experimental dynamic studies of penetration/ cavity expansion physical process
- Computational approaches for material damage modeling and prediction at the micro-scale, meso-scale, and bridging to the continuum scale
- Stochastic considerations to characterize weapon effects / weapon-target interaction
- Experimental or computational approaches to improve simulation of extremely high strain rate mechanics in pre-shocked/pre-stressed geomaterials and concretes



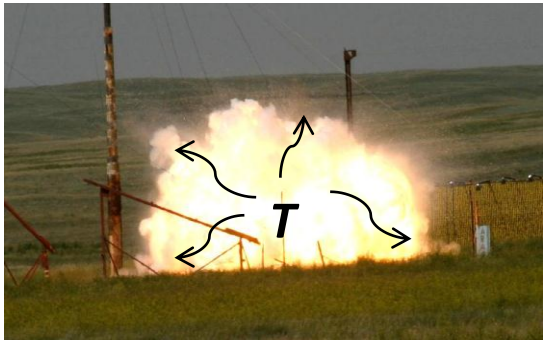
Courtesy of Oleg Vorobiev, LLNL

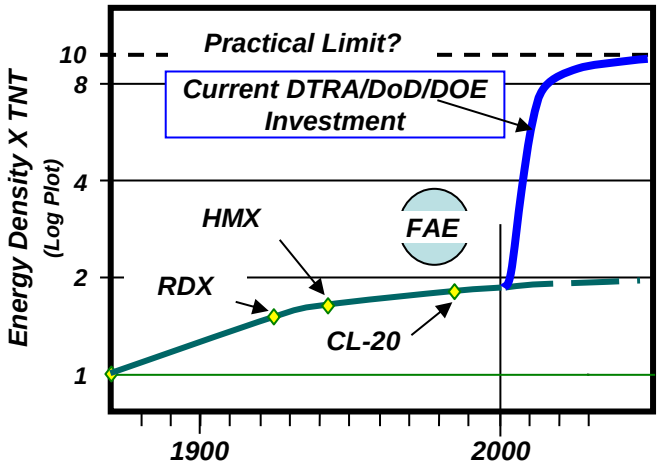
Topic 10: Energetic Materials for CWMD

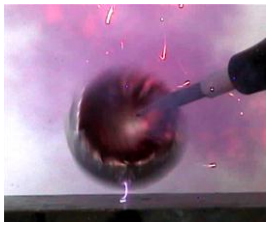
Objective: New energetic materials with high energy density and fast energy release to significantly improve conventional weapons lethality; or reactive materials that produce persistent (milliseconds to seconds) high temperatures (1000ºC or above) and employ chemical kill mechanisms to significantly improve chemical-agent and biological-agent defeat capabilities.

Research areas could include:

- Conglomerations of metal and energetic materials using supra-molecular chemical techniques resulting in an entire formulation in one material that detonates/deflagrate at high temperature and produce chemicals that decompose chemical agents or destroy bio agents
- Novel shock- or detonation-focusing techniques (not shape-charges)
- Demonstration of the effect of these materials, including testing

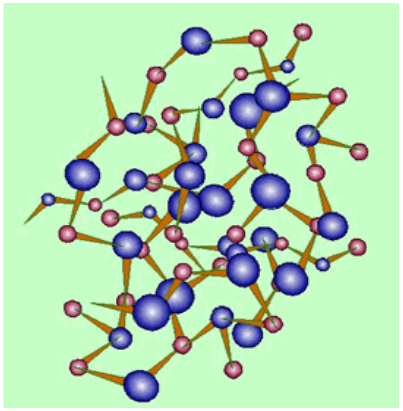






Topic 11: Smart Materials with Unconventional Indicators for Facility Access Denial and Security of WMD Materials

Objective: Unconventional indicators in combination with new smart materials to advance methods to detect, characterize, and control/deny WMD and WMD materials. Combination should detect and characterize the presence of WMD or related activities, then respond to said presence in such a way that prevents it from spreading and controls access in WMD environments.



Research areas could include:

- Exploration of novel materials to seal, encapsulate, or contain WMD vapors or other materials of interest.
- Investigate morphing materials that provide potential for forming expandable, thin membranes or other forms to aid containment including degradation of vital WMD components/equipment or interference with WMD transportation modalities.
- Additional understanding of the properties of materials (including rheology, programmable mater, nano-energetics, energy storage/power transduction) and cues from embedded sensors that enable material flow in response to where WMD presence is tracked to support containment.
- Unconventional indicators of chemical/biological analytes to provide warning of intrusions or presence/movement of WMD, CW/BW precursors, or related equipment of interest
- Additional unconventional indicators (novel ways to measure or sense observables) of CBRNE presence or movement including sensing of environmental disturbances indicating movement or WMD activities

Topic 12: Fundamental Understanding of *in vitro* Glycosylation: Methods, Stability, Immunogenicity, and Efficacy of Therapeutic Glycoproteins

Objective: Proposals are invited that explore human glycan patterns and develop *in vitro* platforms that can modulate recombinant protein glycan structures from any expression system**.** It is preferred that applicants work with model proteins that have prophylactic or therapeutic benefit to the chemical and biological defense medical countermeasures portfolio. Although there have been efforts to engineer human-like post-translational modifications into various expression hosts, these processes involve complex strain engineering and would need to be optimized for each expression host. *In vitro* methods to redecorate recombinant proteins with human-like glycosylation patterns may enable modification of any expressed protein, regardless of the host expression system. This basic research topic is not seeking proposals that involve strain or organism engineering of glycosylation pathways or reengineering of protein sequence to add or remove locations of glycan addition. In addition, work focusing on the addition of non-natural moieties (polymers, other sugars, etc.) not typically found on glycan structures is also outside the scope of this topic. Instead, work proposed should lead to more efficient *in vitro* processes for glycan redecoration and should be compatible with scalable processes.

Research areas could include:

- Exploring the role of glycosylation in general and specifically, sialylation, in fundamental biological processes (efficacy, stability, immunogenicity).
  - Effect of heterogeneity in glycans that could affect process consistency in developing a pharmaceutical
  - Needed pathway for glycan modulation so mechanism of action can be recapitulated *in vitro*
- *In vitro* methodology for homogenous control of glycans on glycoproteins to any expressed protein
  - Stepwise approaches for glycan addition using either enzymes to recapitulate biochemical glycan pathways, or use of chemicals or other abiotic methods for glycan redecoration
  - Work may also include development of more efficient biochemical pathways (e.g. fewer steps or new enzymes) than that found in nature

Topic 13: Predictive Understanding of the Blood-Brain Barrier in Threat Environments
(Chemical & Biological)

Objective:

- Develop predictive understanding of the mechanisms of interaction of the blood-brain barrier with alphaviruses, pesticides, or highly polar molecules
- Enable improved predictive toxicology, risk analysis, and revolutionary strategies to countermeasures available within the central nervous system

Research areas could include:

- Elucidation of mechanisms of transport through the BBB and correlated modulation of neurochemistry/physiology, including differential gene expression, physicochemical or cellular mechanisms, and time-dependent characterization of target pathways subject to modification to alter transport
- Development of in silico models with in vitro validation, accurately predicting human blood-brain barrier transport mechanisms including systemic and environmental factors
- Development and application of non-invasive imaging/ tracking methods to probe local mechanistic phenomena determining molecular and viral distribution

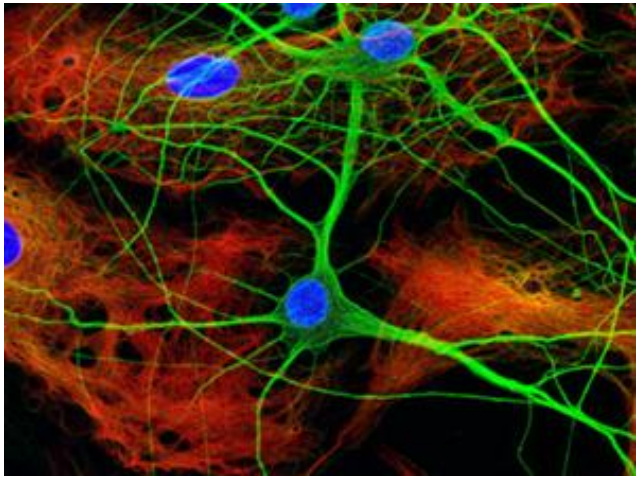


Image source: Babraham Institute, used with permission

Topic 13: Predictive Understanding of the Blood-Brain Barrier in Threat Environments

Objective: Acquire improved fundamental understanding, as demonstrated in part by substantially improved validated predictive capability of *in silico* models, of the mechanisms of interaction of the BBB with alphaviruses, pesticides, or highly polar molecules (*e.g.*, oximes, hydroxamates).

Research areas could include:

- Elucidation of mechanisms of transport through the BBB, together with correlated modulation of neurochemistry and neurophysiology
- Development of *in silico* models with *in vitro* validation that accurately mimic mechanisms of transport across the human BBB and that predict relationships among permeability, active transport, molecular structure and dynamics, together with relevant systemic and environmental factors
- Development and application of dynamic quantitative chemical imaging or non-invasive tracking methods that can probe local mechanistic phenomena determining molecular and viral distribution and penetration across the BBB, with minimal perturbation to the local environment

Topic 14: Bio-inspired Catalytic and Binding/Reporting Systems for Chemical/Biological Defense (CBD)

Objective: Develop fundamental knowledge for reliable and predictive capabilities to model and construct highly efficient, rugged, and inexpensive synthetic functional materials. The topic addresses the following:

1) understanding mechanisms of high efficiency phenomena of bio-systems
2) using acquired knowledge to design / construct more robust / efficient functional mimics
3) identifying new mechanisms that go beyond biomimetics for highly efficient synthetic substitutes

Ultimate goal is to develop reliable capabilities to predict functional efficiency of synthetic mimics and model highly efficient functional molecules

Research areas could include:

- Designed biomaterials: understanding, design, and synthesis of more robust biomaterials with enhanced functionality
  - Enzymes
  - Enhancing biological material properties (e.g., ruggedness)
  - Engineered microbes
- Biomimetics and beyond
  - Enzyme mimics
  - Nucleic acid mimics
- Highest consideration will be given to proposals that combine theory/heuristics and experimental verification with iterative (spiral) approaches to understand the underlying structure-activity relationships

Topic 15: Ambient Surface Chemistry of Chemical Warfare Agent (CWAs) Air Purification Filtration Materials

Objective: Provide improved fundamental understanding of environmental surface reaction and decontamination processes to allow warfighters to address the challenges posed by current and evolving CWA threats. DTRA aims to understand effects of ambient compounds (including environmental and battlefield contaminants) on surface structure, chemistry, and stability of CWA filtration/destruction materials under operational conditions, and use this information to guide new materials strategies for CWA filtration and decomposition. Research will employ ambient surface analytical methods for understanding, *in situ* and *in operando*, surface reaction mechanisms of adsorption, and/or decomposition of CWAs, or their surrogates, on agent filtration materials and destruction catalysts.

- Particular interest in understanding influence of ambient atmosphere, especially H_2O vapor as a function of relative humidity, as well as atmospheric contaminants on surface structure and chemistry of activated carbon materials impregnated with Zn and Cu catalysts, as well as metal oxide filtration materials
- Examples of CWA simulant systems of interest include – but are not limited to:
  - Catalytic oxidation of gaseous sulfur mustard simulant (2-chloroethyle-thylsulfide (CEES)) in the presence of H_2O, NO_x, SO_x, and/or diesel fuel vapor;
  - Catalytic hydrolysis of di-isopropyl fluorophosphonate (DFP) in the presence of dimethyl methylphosphonate (DMMP) and/or of H_2O, NO_x, SO_x.
- Elucidate factors influencing enhancement/degradation of competitive binding or turnover
- Highest consideration will be given to proposals that combine theory and experiment

Topic 16: Gene Amplification and Overexpression: Novel Mechanisms of Multidrug Resistance (MDR) Phenotypes

Objective: Effort should yield knowledge leading to a basis for revolutionary approaches to diagnose and treat MDR infection. Objectives of this topic are to conduct theoretical and experimental research to further fundamental understanding of novel biomarkers of gene amplification and overexpression derived AMR. Emphasis will be on basic mechanisms of AMR derived from gene amplification and overexpression, identification of markers, and development of tools and methods for mechanistic analysis of gene amplification. Due to inherent cell population variability, use of single-cell proteomics, transcriptomics and genomics tools to develop coherent understanding of mechanisms of recently discovered bacterial gene amplification/dosage effects can result in AMR are encouraged.

Bacterial gene amplification/over-expression resistance effect should address:

- Demonstration of one or more novel mechanisms for inducing AMR (e.g. catalytic substrate-binding specificity change)
- Demonstration that mechanism of AMR is induced upon exposure to antimicrobial compounds
- Demonstration of quantitative or threshold effects that may be leveraged to estimate MIC of antibiotics
- Determination if gene amplification is associated with point mutations
- Determination if gene amplification is linked to horizontal transfer or if it creates susceptibility to horizontally transferred plasmids
- Demonstration of housekeeping genes that are up-regulated/down-regulated
- Demonstration of host miRNA changes, that may indicate presence of AMR or MDR infection involvement
- Demonstrate if over-expressed proteins are preferentially modified to incur MDR behavior
- Demonstration that this mechanism may be able to confer not only AMR, but also MDR phenotype (i.e. could this be a broad protective mechanism).

Topic 17: WMD Signal Transducer Toolkit for Synthetic Biology Applications

Objective: Solicitation is to develop knowledge base and potential new approaches to establish suite of biological transducers - proteins that bind an analyte and initiate a response cascade - specific to chemical weapon nerve agent targets. Potential transducers might include but are not limited to, periplasmic-binding proteins, extracellular receptors and DNA-binding proteins. Proposals must justify the chosen model organism and its potential utility for synthetic biology applications

Research areas could include:

- Discover potential novel platforms for further engineering, projects are sought which develop new understanding of or identify naturally occurring pairs of receptors and their genetic response pathway. To demonstrate new knowledge, proposals must show that screened transducers can receive (sense target molecule) and transmit (initiate a cellular response). Efforts will be favored that focus on identifying response elements with receptors that bind small molecules similar to organophosphorous nerve agents.
- Explore feasibility of creating novel signal transducers responsive to chemical nerve agents - projects are sought which engineer currently known receptors to recognize nerve agents or surrogates. Strategies may include, but are not limited to, engineering existing receptors or creating fusion proteins with binding and signal components from separate proteins. Proposals must include methods to measure binding affinity and to demonstrate specificity for nerve agent or surrogate chosen. Engineered proteins must also demonstrate the ability to initiate a cellular response *in vivo*.

Proposals that primarily focus on creating novel sensor pathways, rather than identifying and establishing novel transducing elements, will not be funded. Proposals which exclusively use *in silico* techniques without experimental validation will also not be considered.

Summary

- DTRA is dedicated to
  - Long-term research and development to Counter-WMD
  - Training of next generation workforce
  - University engagement
- The final number of grants and the amount of funds allocated for this period will be determined after all pre-application white papers and invited proposals are received and evaluated.

Foster and enable farsighted, high-payoff research

Discussion and Q&A